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Association between Anxiety Disorders and Heart Rate Variability in The Netherlands Study of Depression and Anxiety (NESDA)

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Objective: To determine whether patients with different types of anxiety disorder (panic disorder, social phobia, generalized anxiety disorder) have higher heart rate and lower heart rate variability compared with healthy controls in a sample that was sufficiently powered to examine the confounding effects of lifestyle and antidepressants. **Methods:** The standard deviation of the normal-to-normal intervals (SDNN), heart rate (HR), and respiratory sinus arrhythmia (RSA) were measured in 2059 subjects (mean age = 41.7 years, 66.8% female) participating in The Netherlands Study of Depression and Anxiety (NESDA). Based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and Composite International Diagnostic Interview (CIDI), NESDA participants were classified as healthy controls (n = 616), subjects with an anxiety diagnosis earlier in life (n = 420), and subjects with current anxiety diagnosis (n = 1059). **Results:** Current anxious subjects had a significantly lower SDNN and RSA compared with controls. RSA was also significantly lower in remitted anxious subjects compared with controls. These associations were similar across the three different types of anxiety disorders. Adjustment for lifestyle had little impact. However, additional adjustment for antidepressant use reduced all significant associations between anxiety and HRV to nonsignificant. Anxious subjects who used a tricyclic antidepressant, a selective serotonin reuptake inhibitor, or another antidepressant showed significantly lower mean SDNN and RSA compared with controls (effect sizes = 0.20–0.80 for SDNN and 0.42–0.79 for RSA). Nonmedicated anxious subjects did not differ from controls in mean SDNN and RSA. **Conclusion:** This study shows that anxiety disorders are associated with significantly lower HR variability, but the association seems to be driven by the effects of antidepressants. **Key words:** anxiety disorder, SDNN, RSA, cardiac vagal control, heart rate, antidepressants.

ANOVA = analysis of variance; **ANS** = autonomic nervous system; **ATC** = anatomical therapeutic chemical; **BAI** = Beck Anxiety Inventory; **BMI** = body mass index; **CIDI** = Composite International Diagnostic Interview; **CVD** = cardiovascular disease; **dZ** = changes in thorax impedance; **ECG** = electrocardiogram; **GAD** = generalized anxiety disorder; **HR** = heart rate; **HRV** = heart rate variability; **IBI** = inter-beat-interval; **MDD** = major depressive disorder; **MET** = multiple of one's resting metabolic rate times minutes of physical activity; **NESDA** = The Netherlands Study of Depression and Anxiety; **PD** = panic disorder; **pv** = peak-valley; **PNS** = parasympathetic nervous system; **RR** = respiratory rate; **RSA** = respiratory sinus arrhythmia; **SDNN** = standard deviation of the normal-to-normal interval; **SNS** = sympathetic nervous system; **SP** = social phobia; **VU-AMS** = Vrije Universiteit Ambulatory Monitoring System; **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant.

INTRODUCTION

Anxiety disorders have been associated with an increased risk of cardiovascular morbidity and mortality (1–10). One of the hypothesized causes for this association is a dysregulation of the autonomic control of the heart because autonomic nervous system (ANS) activity is associated with cardiovascular disease (CVD) and mortality (11–15) as well as anxiety disorders. Episodic acute "state" anxiety is characterized by an increase in heart rate (HR) paired to a decrease in total HR variability (HRV) and respiratory sinus arrhythmia (RSA) (16–18). The latter is often seen as the best available proxy for cardiac vagal control (19,20). Lower total HRV and cardiac vagal control are also found in subjects reporting chronic levels of anxiety, as assessed by "trait anxiety" inventories (21,22) and in patients with a clinical anxiety disorder (23–27). A recent review by Friedman (22) suggested that RSA is lowered most strongly in patients with panic disorder (PD), when compared with social phobia and generalized anxiety disorder. Friedman's review also detected substantial heterogeneity in the outcome across studies.

A potential limitation of the studies in clinical samples so far is that they were relatively small and, as a consequence, could not take into account potential confounders of the relationship between anxiety and HRV. Specifically, lifestyle factors and the use of psychoactive medication have not been taken into account in most of the studies to date. With regard to the latter, we recently showed that antidepressants had a major lowering impact on standard deviation of the normal-to-normal interval (SDNN) and RSA in depressed patients (28). The present study examines HR, SDNN, and RSA in subjects with a current or remitted anxiety diagnosis and healthy controls. The study was sufficiently powered to examine the extent to which a potential association between anxiety disorder and HR and HRV is confounded by a number of lifestyle factors and the use of antidepressants. We also examined whether differences in HR, SDNN, and RSA were

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consistent across different anxiety disorders (PD, social phobia, and generalized anxiety disorder) and whether these differences were larger for anxiety patients with a current diagnosis compared with those with a remitted diagnosis.

METHODS

Subjects

Subjects participating in the present study came from The Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study conducted among 2981 adult subjects (age = 18–65 years) to examine the long-term course of depression and anxiety disorders. The rationale, methods, and recruitment strategy have been described elsewhere (29). The NESDA sample consists of 652 persons without depression or anxiety disorders and 2329 with a (remitted or current) diagnosis of depressive or anxiety disorder. To represent various settings and stages of psychopathology, depressed or anxious subjects were recruited at three different locations in The Netherlands in different settings: community, primary care, and mental healthcare organizations. Community-based subjects had previously been identified in a population-based study, primary care subjects were identified through a three-stage screening procedure (involving the K10 (30) and the short-form Composite International Diagnostic Interview (CIDI) psychiatric interview by phone) conducted among patients of 65 General Practitioners; and mental healthcare patients were recruited when newly enrolled at one of the 17 participating mental health organization locations.

NESDA subjects were assessed between September 2004 and February 2007 during a 4-hour visit to one of the seven field center locations. During this visit, the presence of anxiety disorders was ascertained using the lifetime version of the CIDI psychiatric interview (World Health Organization (WHO) version 2.1). The CIDI establishes diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria (31) and has shown high interrater and test-retest reliability and high validity for anxiety disorders (32). In addition, the severity of anxiety was measured among all subjects using the Beck Anxiety Inventory (BAI) (33).

To test whether HR, SDNN, and RSA differed across persons with and without an anxiety disorder, three clearly distinct anxiety groups were created for the present study. The first group consisted of 616 control subjects with no history of any anxiety disorders, depression, or other psychiatric disorders. The second group consisted of 420 persons with an anxiety disorder-diagnosis (as defined by the CIDI) earlier in life but not in the past 6 months. This group was referred to as the remitted anxiety group. The third group—referred to as the current anxiety group—consisted of 1159 persons with a CIDI-confirmed anxiety disorder in the past 6 months (84% had experienced an anxious episode in the past month). The remaining 786 NESDA subjects were excluded from the analyses: 688 patients had a depressive disorder in absence of an anxiety disorder; 98 subjects had missing physiological data due to equipment failure during assessment or poor electrocardiogram (ECG) quality.

For additional analysis on anxiety subtype, the 1479 anxious subjects (remitted + current) were further classified based on the CIDI data, in three variables assessing the presence or absence of remitted or current PD, remitted or current social phobia (SP), and remitted or current generalized anxiety disorder (GAD).

Measurements

The clinic visit consisted of a blood draw, a medical examination, supine rest with blood pressure recordings, psychiatric interviews, a cognitive computer task, saliva collection, and administration of several written questionnaires concerning mood state, lifestyle, medical history, and actual medication use. Extensive information about psychological, biological, physical, and demographic determinants was collected. The study protocol was approved centrally by the Ethical Review Board of the VU University Medical Center and subsequently by local review boards of each participating center. All subjects signed an informed consent at baseline assessment.

Physiological Measurement

HR and SDNN were assessed using a three-lead ECG signal that was measured by the VU-AMS. The VU-AMS is a light-weight ambulatory device that records the ECG and changes in thorax impedance (dZ) from six electrodes placed on the chest and back of the subjects (34,35). The respiration signal is obtained from the filtered (0.1–0.4 Hz) dZ signal. An automatic scoring algorithm detects the beginning and end of inspiration and expiration and computes the respiratory rate (RR) from these values. RSA was assessed by peak-valley estimation (pvRSA) using the combined ECG and dZ signals. Per breath, estimates of pvRSA were obtained by subtracting the shortest inter-beat-interval (IBI) during HR acceleration in the inspirational phase (which was made to include 750 milliseconds from the following expiration to account for phase shifts) from the longest IBI during deceleration in the expirational phase (including 750 milliseconds from the following expiratory pause/inspirational phase). When no phase-related acceleration or deceleration was found, the breath was assigned a pvRSA score of zero. Automatic scoring of RR and pvRSA was checked by visual inspection of the respiratory signal and IBI time series from the entire recording. Breathing cycles that showed irregularities like gasps, breath holding, coughing or that had IBI artifacts (ectopic beats or too long beats due to failed R-wave detection) were not considered valid and were rejected and removed from further processing. In the remaining data, the shortest and longest breaths as well as the breaths containing the shortest and longest IBIs (defined by 3 SD from the mean in either direction) were automatically removed from the entire recording before averaging pvRSA across all remaining breaths to a single mean pvRSA for each of the labeled periods. In total, 74 subjects were removed from the final data set because >25% of their breaths were discarded during automated or visual data cleaning (36,37). RSA can alternatively be assessed as the high-frequency power of the IBI time series by Fourier or Wavelet-analysis (38) but it has been shown that the time and frequency domain measures essentially pick up the same between-subject variation and can be used interchangeably (37,39). The advantage of pvRSA assessments is that they additionally yield the RR.

Recording is unobtrusive and subjects, who maintain full freedom of movement, tend to habituate very rapidly to this type of recording. NESDA subjects were wearing the VU-AMS device during a large part of the NESDA clinic visit, at the same time participating in the different assessment parts. The start of the various assessment stages was marked with an event marker to divide the total recording into fixed periods (resting baseline, breaks, interview 1, computer task, interview 2). Movement registration through vertical accelerometry was used to excise periods where subjects were nonstationary. Removal of breaks and nonstationary parts (about 15 minutes) resulted in the four conditions used in the final analyses: a supine rest condition with three blood pressure measurements (9.7 ± 3.0 minutes), and three conditions with mild cognitive load in which the subjects were sitting upright: interview session 1 (investigating somatic health; functioning and healthcare utilization; sitting, 38.2 ± 12.7 minutes); interview session 2 (investigating family and personal history and life events; sitting, 35.6 ± 12.7 minutes); and a computer task (Implicit Association Task; sitting, 16.2 ± 4.0 minutes). The Implicit Association Task is a computerized task designed to measure implicit associations between self items, on the one hand, and anxiety-related and depression-related items, on the other hand (40).

Covariates

RR has often been associated with HRV and several studies suggested that research investigating HRV should take RR into account (34,41). Therefore, we adjusted analyses for RR. Sociodemographics included age, sex, and education in years. In addition, various health indicators were considered as covariates because these have been linked with both anxiety and ANS activity. Body mass index (BMI) was determined as measured weight in kilograms divided by the square of the measured height in meters. Physical activity was measured using the International Physical Activity Questionnaire (42) and expressed in MET-minutes per week (the multiple of one's resting metabolic rate times minutes of physical activity per week). Smoking status was defined as a dichotomous variable; nonsmoker versus smokers. Three categories were created for alcohol use: nondrinker, mild-to-moderate drinker

TABLE 1. Main Sample Characteristics for Controls and Anxious Subjects

Variable[a]	Control (n = 616)	Remitted Anxiety (n = 421)	Current Anxiety (n = 1159)	p^a
Age, years (mean ± SD)	41.1 ± 14.7	43.6 ± 12.6	40.9 ± 12.3	.001
Sex, % (female)	61	70.5	68.1	.002
Education, years (mean ± SD)	12.8 ± 3.2	12.5 ± 3.1	11.6 ± 3.3	<.001
BMI (mean ± SD)	25.1 ± 4.6	25.7 ± 5.0	25.6 ± 5.2	.06
Physical activity, 1000 MET min/week (mean ± SD)	3.8 ± 3.1	3.6 ± 2.8	3.6 ± 3.1	.28
Smoking (% yes)	25.9	32.3	46.6	<.001
Alcohol use (%)				
Nondrinker	11	15.2	22	<.001
Mild/moderate drinker	71.2	69.8	62.6	
Heavy drinker	17.8	15	15.4	
β ($\sigma\epsilon\psi$ %) $\sigma\tau\nu\epsilon\gamma\alpha$ $\gamma\nu\iota\kappa\chi o\lambda\beta$	6.5	9	8	.29
Other heart or blood pressure medication (% yes)	11.7	11.2	9.7	.4
Heart or coronary disease (% yes)	4.7	5.5	6.3	.38
Chronic diseases (mean nr. ± SD)	1.01 ± 1.1	1.30 ± 1.2	1.37 ± 1.3	<.001
Medication use				
Tricyclic antidepressants (% yes)	0	2.9	4.2	<.001
Selective serotonin reuptake inhibitors (% yes)	0	15.9	27.1	<.001
Other antidepressants (% yes)	0	3.8	9.5	<.001
Comorbid major depressive disorder	0	75.3	79.4	<.001
Panic disorder[b]				
Remitted (% yes)	0	35.2	4.4	<.001
Current (% yes)	0	0	55.4	
Social phobia[b]				
Remitted (% yes)	0	41.1	5.1	<.001
Current (% yes)	0	0	55.5	
Generalized anxiety disorder[b]				
Remitted (% yes)	0	48.7	8.8	<.001
Current (% yes)	0	0	38.2	
Respiratory rate,[c] breaths per minute (mean ± SD)	17.2 ± 1.2	17.0 ± 1.1	17.1 ± 1.2	.02
BAI score (mean ± SD)	4.0 ± 4.8	9.2 ± 7.6	18.9 ± 10.9	<.001

[a] Comparison using analysis of variance analyses (continuous variables) and χ^2 statistics (categorical variable).
[b] Percentages anxiety disorders do not add up due to comorbidity.
[c] Respiratory rate is averaged over rest and test conditions.
SD = standard deviation; MET = multiple of the resting metabolic rate; BAI = Beck Anxiety Inventory.

(<14 glasses a week), and heavy drinker (≥14 glasses a week). Self-reports were used for ascertainment of the presence of heart disease (including coronary disease, cardiac arrhythmia, angina, heart failure, and myocardial infarction) and other chronic conditions (epilepsy, diabetes, osteoarthritis, stroke, cancer, chronic lung disease, thyroid disease, liver disease, chronic fatigue syndrome, intestinal disorders, and ulcer). Furthermore, it was determined whether subjects were using heart medication by copying the names of medicines from the containers brought in by the subjects. We classified medication using the WHO Anatomical Therapeutic Chemical (ATC) classification (43). First, a dichotomous variable for the use of β blockers was computed, scoring "yes" if subjects frequently (daily or >50% of the time) used a medication with ATC code starting with: C07 (β blocking agents). A second variable was made for the use of other heart medication using ATC codes starting with: C01 (cardiac therapy), C02 (antihypertensives), C03 (diuretics), C04 (peripheral vasodilators), C05 (vasoprotectives), or C08 (calcium-channel blockers).

In addition, we conducted additional analyses with covariates that may further explain a potential association between anxiety and HR and HRV function. First, because we recently found that antidepressants had a major lowering impact on SDNN and RSA in depressed patients (28), frequent use (daily or >50% of the time) of antidepressant medication was considered as covariate. We distinguished selective serotonin reuptake inhibitors (SSRIs) (ATC code N06AB), tricyclic antidepressants (TCAs) (ATC code N06AA), and other antidepressants (including monoamine oxidase inhibitors, nonselective N06AF, and antidepressants classified as N06AX). Second, we explored whether the association between anxiety disorder and HR and HRV was explained by the presence of comorbid remitted or current major depressive disorder (MDD) as assessed using the CIDI psychiatric interview. Third, the importance of two indicators of severity of anxiety (BAI score and number of anxiety disorders present) in the association with HR and HRV was examined.

Statistical Analyses

Data were analyzed using SPSS 15.0. Characteristics across the three anxiety groups (controls, remitted, and current anxiety) were compared using analysis of variance (ANOVA) and χ^2 statistics. Mixed model analysis showed that differences in ANS measures between anxiety groups were similar for the computer task and interview parts and data during the computer task and interview parts were collapsed to create a single "test" condition to simplify analyses. ANOVAs were conducted separately for the rest and test conditions to compare HR, SDNN, and RSA between the anxiety groups. These analyses were repeated with consideration of covariates (RR, age, sex, education, BMI, smoking, alcohol use, physical activity, heart disease, heart medication, and chronic disease count). Subsequently, the role of two main explanatory variables (antidepressant medication and comorbid major depressive disorder) was examined by entering information on these variables in the analyses of covariance.

TABLE 2. Heart Rate (bmp), SDNN (ms), and RSA (ms) in Control and Anxiety Disorders, Raw and Adjusted for Covariates

	Control (n = 616)	Remitted Anxiety Disorder (n = 420)	Control Versus Remitted Anxiety Disorder	Effect Sizes Control Versus Remitted Anxiety	Current Anxiety Disorder (n = 1159)	Control Versus Current Anxiety Disorder	Effect Size Control Versus Current Anxiety
Rest condition							
Heart rate (mean ± SE)							
Unadjusted	68.4 ± 0.4	68.8 ± 0.5	0.61	0.032	69.3 ± 0.3	0.05	0.096
Basic adjustment[a]	68.5 ± 0.4	68.8 ± 0.5	0.65	0.029	69.1 ± 0.3	0.22	0.062
Full adjustment[b]	68.7 ± 0.4	68.8 ± 0.5	0.84	0.013	69.0 ± 0.3	0.51	0.033
+Adjustment for antidepressant use	69.0 ± 0.4	69.0 ± 0.5	0.95	0.004	68.8 ± 0.3	0.75	0.017
SDNN (mean ± SE)							
Unadjusted	79.1 ± 1.3	74.3 ± 1.6	0.02	0.146	72.9 ± 1.0	<0.001	0.189
Basic adjustment[a]	78.5 ± 1.2	76.3 ± 1.5	0.26	0.071	72.5 ± 0.9	<0.001	0.199
Full adjustment[b]	77.7 ± 1.2	76.3 ± 1.5	0.46	0.047	73.0 ± 0.9	0.002	0.156
+Adjustment for antidepressant use	75.6 ± 1.3	75.7 ± 1.4	0.94	0.005	74.2 ± 0.9	0.40	0.044
RSA (mean ± SE)							
Unadjusted	51.3 ± 1.3	45.0 ± 1.5	0.002	0.200	45.4 ± 0.9	<0.001	0.188
Basic adjustment[a]	51.6 ± 1.1	46.9 ± 1.3	0.005	0.182	44.5 ± 0.8	<0.001	0.273
Full adjustment[b]	51.4 ± 1.1	47.0 ± 1.3	0.009	0.165	44.7 ± 0.8	<0.001	0.250
+Adjustment for antidepressant use	48.5 ± 1.1	46.4 ± 1.3	0.21	0.079	46.3 ± 0.8	0.12	0.082
Test condition							
Heart rate (mean ± se)							
Unadjusted	73.4 ± 0.4	72.6 ± 0.5	0.20	0.083	73.1 ± 0.3	0.46	0.037
Basic adjustment[a]	73.5 ± 0.4	72.9 ± 0.5	0.31	0.064	73.0 ± 0.3	0.30	0.052
Full adjustment[b]	73.5 ± 0.4	72.9 ± 0.5	0.32	0.062	72.9 ± 0.3	0.24	0.060
+Adjustment for antidepressant use	73.6 ± 0.4	73.0 ± 0.5	0.33	0.061	72.9 ± 0.3	0.13	0.079
SDNN (mean ± SE)							
Unadjusted	65.6 ± 0.9	63.9 ± 1.1	0.23	0.077	62.8 ± 0.7	0.02	0.123
Basic adjustment[a]	65.4 ± 0.9	65.1 ± 1.0	0.86	0.011	62.5 ± 0.6	0.007	0.138
Full adjustment[b]	64.9 ± 0.9	65.1 ± 1.0	0.91	0.007	62.7 ± 0.6	0.04	0.104
+Adjustment for antidepressant use	63.4 ± 0.9	64.6 ± 1.0	0.36	0.058	63.6 ± 0.6	0.85	0.010
RSA (mean ± SE)							
Unadjusted	46.6 ± 1.0	42.4 ± 1.3	0.01	0.168	43.4 ± 0.8	0.01	0.128
Basic adjustment[a]	47.1 ± 0.9	44.2 ± 1.1	0.04	0.124	42.5 ± 0.6	<0.001	0.182
Full adjustment[b]	47.1 ± 0.9	44.2 ± 1.1	0.03	0.120	42.5 ± 0.7	<0.001	0.175
+Adjustment for antidepressant use	45.1 ± 0.9	43.6 ± 1.0	0.31	0.074	43.7 ± 0.7	0.25	0.062

[a] Adjusted for respiratory rate, age, sex, and education.
[b] Additionally adjusted for body mass index, physical activity, smoking, alcohol use, chronic disease, β blocking agents, other heart medication, and heart disease.
SDNN = root mean square of successive differences; RSA = respiratory sinus arrhythmia; SE = standard error.

To examine whether different anxiety disorders had differential associations with HR and HRV, we conducted multivariate regression analyses on HR, SDNN, and RSA including covariates and anxiety subtype indicators. Finally, we distinguished anxious with and without various types of psychoactive medication and compared their HR, SDNN, and RSA with those of controls in fully corrected analyses of covariance (ANCOVAs). Effect sizes were calculated with Cohen's d (1988) defined as the difference in the mean RSA, SDNN, and HR between two groups, divided by the pooled standard deviation (SD) of these groups.

RESULTS

The mean ± SD age of the study sample (n = 2195) was 41.7 ± 13.1 years, 66.8% was female, and 50.9% had <12 years of education. Table 1 shows the demographic characteristics, disease status, lifestyle habits, and medication use according to anxiety diagnosis. Of the individuals with a current anxiety disorder, 55.4% had a PD, 55.5% had a social phobia, and 38.2% had a generalized anxiety disorder. Compared with the nonanxious subjects, anxious subjects were more likely to be female, had less education, had a higher BMI, were more likely to smoke but less likely to drink, had more chronic diseases, were more likely to use antidepressants, had a lower RR, and had a higher BAI score.

Table 2 presents the results of the unadjusted and adjusted ANOVA analyses on HR, SDNN, RSA for anxiety status for the rest and test conditions. Results showed that HR did not differ in either condition between current or remitted anxious subjects and healthy controls, independent of covariates. For

TABLE 3. Results of Regression Analyses Predicting Heart Rate (bpm), SDNN (ms), and RSA (ms) Among Controls and Anxious Subjects

	Heart Rate			SDNN			RSA		
	B	*p*	R^2	B	*p*	R^2	B	*p*	R^2
Rest condition									
Model 1			.097			.205			.324
Respiratory rate (per 1 breath per minute increase)	0.452	<.001		−1.745	<.001		−3.063	<.001	
Age (per 1 year increase)	−0.040	.03		−0.988	<.001		−1.319	<.001	
Sex (female versus male)	2.498	<.001		−6.111	<.001		7.706	<.001	
Education (per 1 year increase)	−0.068	.29		−0.180	.38		−0.276	.13	
Physical activity (per 1000 MET-minutes a week increase)	−0.171	.07		0.370	.07		0.159	.39	
BMI (per 1 kg/m^2 increase)	0.285	<.001		−0.574	<.001		−0.405	.001	
Heavy alcohol use versus no alcohol use	−1.735	.02		5.971	.009		5.690	.005	
Mild/moderate alcohol use versus no alcohol use	−1.799	.001		7.279	<.001		4.904	.002	
Smoking (yes versus no)	1.107	.01		−1.435	.30		0.377	.76	
Chronic disease (per 1 disease increase)	−0.139	.42		−0.067	.90		0.576	.24	
Heart disease (yes versus no)	0.654	.49		−2.120	.49		−1.936	.47	
β-blocking agents (yes versus no)	−7.341	<.001		0.874	.75		2.318	.34	
Other heart medication (yes versus no)	2.257	.003		−2.095	.39		0.468	.83	
Current panic disorder (yes versus no)	−0.226	.64		−2.639	.08		−3.066	.02	
Remitted panic disorder (yes versus no)	0.306	.67		−4.004	.08		−4.053	.05	
Current social phobia (yes versus no)	0.349	.45		−3.071	.04		−4.471	.001	
Remitted social phobia (yes versus no)	−0.256	.71		1.352	.53		−2.786	.14	
Current generalized anxiety disorder (yes versus no)	.0.079	.88		−3.648	.03		−2.242	.13	
Remitted generalized anxiety disorder (yes versus no)	−0.148	.80		0.660	.73		−0.542	.75	
Model 2 (Model 1 + antidepressant use)[a]			.118			.222			.349
Current panic disorder (yes versus no)	−0.412	.40		−0.804	.60		−0.234	.86	
Remitted panic disorder (yes versus no)	0.209	.77		−2.632	.25		−1.915	.34	
Current social phobia(yes versus no)	0.138	.77		−1.882	.20		−0.2.777	.03	
Remitted Social Phobia (yes versus no)	−0.359	.59		2.246	.30		−1.245	.51	
Current generalized anxiety disorder (yes versus no)	−0.130	.81		−1.837	.27		0.122	.93	
Remitted generalized anxiety disorder (yes versus no)	−0.257	.59		1.513	.42		0.669	.68	
Use of a tricyclic antidepressant (yes versus no)	7.811	<.001		−15.340	<.001		−15.334	<.001	
Use of a selective serotonin reuptake inhibitor (yes versus no)	−0.182	.75		−5.191	.004		−10.500	<.001	
Use of an other antidepressant (yes versus no)	3.054	.001		−15.263	<.001		−14.284	<.001	
Test condition									
Model 1			.123			.191			.313
Respiratory rate (per 1 breath per minute increase)	1.098	<.001		−2.750	<.001		−3.770	<.001	
Age (per 1 year increase)	−0.085	<.001		−0.647	<.001		−1.045	<.001	
Sex (female versus male)	2.306	<.001		−3.575	<.001		6.906	<.001	
Education (per 1 year increase)	−0.059	.36		0.117	.41		−0.038	.80	
Physical activity (per 1000 MET-minutes a week increase)	−0.185	.005		0.272	.06		0.098	.52	
BMI (per 1 kg/m^2 increase)	0.179	<.001		−0.397	<.001		−0.174	.09	
No alcohol use versus heavy alcohol use	−0.926	.20		2.611	.10		2.242	.19	
No alcohol use versus mild/moderate alcohol use	−1.271	.02		3.022	.01		2.991	.02	
Smoking (yes versus no)	0.111	.80		−1.399	.15		1.410	.16	
Chronic disease (per 1 disease increase)	−0.040	.82		0.103	.79		0.366	.37	
Heart disease (yes versus no)	0.562	.56		−0.821	.71		−0.663	.77	
β-blocking agents (yes versus no)	−9.180	<.001		2.526	.19		2.123	.30	
Other heart medication (yes versus no)	2.207	.004		−2.745	.11		−0.797	.66	
Current panic disorder (yes versus no)	−0.784	.10		−0.968	.36		−2.345	.04	

(*Continued*)

TABLE 3. Continued

	Heart Rate			SDNN			RSA		
	B	*p*	R^2	B	*p*	R^2	B	*p*	R^2
Remitted panic disorder (yes versus no)	−0.083	.91		−0.865	.59		−2.400	.15	
Current social phobia (yes versus no)	0.094	.84		−1.092	.29		−2.222	.04	
Remitted social phobia (yes versus no)	0.061	.93		−1.767	.24		−3.158	.05	
Current generalized anxiety disorder (yes versus no)	0.233	.65		−3.177	.007		−3.516	.004	
Remitted generalized anxiety disorder (yes versus no)	−1.020	.08		1.573	.23		−0.833	.55	
Model 2 (Model 1 + antidepressant use)[a]			.145			.213			.333
Current panic disorder (yes versus no)	−0.732	.13		0.261	.81		−0.433	.70	
Remitted panic disorder (yes versus no)	0.003	.99		0.059	.97		−0.970	.56	
Current social phobia (yes versus no)	−0.005	.99		−0.186	.86		−1.003	.36	
Remitted social phobia (yes versus no)	0.068	.92		−1.106	.46		−2.092	.18	
Current generalized anxiety disorder (yes versus no)	0.217	.68		−1.995	.09		−1.906	.12	
Remitted Generalized anxiety disorder (yes versus no)	−1.038	.08		2.192	.09		0.028	.98	
Use of a tricyclic antidepressant (yes versus no)	8.101	<.001		−16.159	<.001		−14.943	<.001	
Use of a selective serotonin reuptake inhibitor (yes versus no)	−1.163	.04		−3.638	.004		−6.937	<.001	
Use of another antidepressant (yes versus no)	1.975	.02		−9.286	<.001		−9.873	<.001	

[a] Model 2 included all covariates of Model 1 as well as antidepressant use variables. Regression coefficients are only shown for anxiety and antidepressant use variables.

MET = multiple of the resting metabolic rate; RSA = respiratory sinus arrhythmia; SDNN = root mean square of successive differences; bpm, beats per minute; ms = milliseconds; BMI = body mass index.

SDNN, a significant difference was found between the current anxious subjects and the controls in both conditions (in the adjusted model, $.002 < p < .04$ and $.104 <$ Cohen's $d < 0.156$) and for RSA, significant differences were found between the controls and both the current and the remitted anxious subjects for both the rest ($p < .001$, Cohens $d = 0.175–0.250$) and test ($.009 < p < .03$, Cohen's $d = 0.120–0.165$) conditions in the fully adjusted model. Additional correction for the BAI score did not change results. Table 2 shows that, in case of SDNN as well as RSA, correction for antidepressant use reduced the differences between the anxiety groups and the control group to nonsignificant.

Table 3 presents the results of the nominal linear regression analyses using the separate anxiety disorders as independent predictors of HR, SDNN, and RSA. Model 1 includes all possible predictors and Model 2 additionally includes the use of different antidepressants. HR was not significantly different from controls in the rest or test condition in any of the three anxiety disorders. However, current anxiety disorders were associated with significantly lower SDNN and RSA, and RSA was also significantly lower in subjects with remitted anxiety disorders. Model 2 shows that all these associations became nonsignificant after adding TCA, SSRI, and other antidepressant use to the model. The use of especially a TCA had a major effect on both SDNN (for the rest and test conditions, $B = -15.340$ and $B = -16.159$, $p < .001$), and RSA ($B = -14.943$ and $B = -15.334$, $p < .001$). The use of an SSRI or other antidepressant also showed this effect, although with a more modest effect size (B values range = −3.638 to −15.263; *p* values range = .004 to ≤.001). Significant effects of antidepressant use were also found for HR; the use of a TCA or other antidepressant increased HR (for the rest and test conditions, respectively, $B = 7.811$ to $B = 8.101$, $p < .001$; and $B = 1.975$ to $B = 3.054$, $p = .02–0.001$). Additional correction for comorbid depression did not change these effects as comorbid depression itself was not significantly associated with SDNN and RSA. Repeating the regression analyses in Table 3 with RSA divided by the IBI (as suggested by Grossman and Kollai) (44) yielded essentially identical results.

Because the regression analyses (Table 3) showed strong effects of antidepressants on the cardiac measures, we decided to analyze further the differences in HR, SDNN, and RSA between controls, anxious subject without medication and anxious subject on TCAs, SSRIs, and other antidepressants. Eventually, five groups of anxiety subjects were distinguished: 326 remitted anxious subjects without medication; 701 current anxious subjects without medication; 60 anxious subjects on a TCA; 376 anxious subjects on a SSRI (no TCA users); and 116 anxious subjects on other antidepressants (no TCA or SSRI users). ANCOVAs were performed to compare these groups with each other on mean HR, SDNN, and RSA. Table 4 provides the main characteristics of the anxious subjects with and without medication. Medicated anxious indi-

TABLE 4. Main Sample Characteristics for Anxious Subjects Taking and Not Taking Antidepressants

	Current Anxiety No Medication (n = 701)	Anxiety on TCA (n = 61)	Anxiety on SSRI (n = 380)	Anxiety on Other Antidepressants (n = 118)	p^a
Age, years (mean ± SD)	40.2 ± 12.8	47.2 ± 10.4	41.4 ± 11.6	43.2 ± 10.9	<.001
Sex, % (female)	69.5	73.8	69.7	60.2	.16
Education, years (mean ± SD)	11.7 ± 3.3	11.2 ± 3.5	11.7 ± 3.3	11.7 ± 3.2	.73
BMI (mean ± SD)	25.2 ± 4.9	27.4 ± 6.2	26.3 ± 5.7	25.9 ± 5.5	<.001
Physical activity, 1000 MET min/week (mean ± SD)	3.8 ± 3.2	2.8 ± 2.5	3.5 ± 3.2	3.1 ± 3.1	.03
Smoking, % yes	43.7	52.5	45.5	52.5	.22
Alcohol use, %					
Nondrinker	18.3	37.7	25.8	26.3	.001
Mild/moderate drinker	64.9	49.2	59.5	65.3	
Heavy drinker	16.8	13.1	14.7	8.5	
β-blocking agents (%yes)	7.2	14.8	7.4	12.7	.05
Other heart or blood pressure medication, % yes	8.3	21.3	8.9	15.3	.002
Heart or coronary disease, % yes	5.4	6.6	6.6	5.1	.86
Chronic diseases (mean nr. ± SD)	1.35 ± 1.2	1.64 ± 1.6	1.33 ± 1.3	1.47 ± 1.4	.28
Medication use					
TCAs, % yes	0	100	0	0	<.001
SSRIs, % yes	0	6.6	100	0	<.001
Other antidepressants, % yes	0	3.3	2.1	100	<.001
Comorbid major depressive disorder	72.6	88.5	89.7	91.5	<.001
Panic disorder[b]					
Remitted, % yes	4.2	9.8	13.7	11	<.001
Current, % yes	50.7	42.6	53.4	51.7	.45
Social phobia[b]					
Remitted, % yes	4.2	13.1	14.5	7.6	<.001
Current, % yes	56	47.5	45.5	44.9	.004
Generalized anxiety disorder[b]					
Remitted, % yes	8.9	16.4	15.3	14.4	.007
Current, % yes	35.4	24.6	33.7	44.9	.04
BAI score (mean ± SD)	17.6 ± 10.7	20.0 ± 12.4	19.4 ± 11.4	19.7 ± 10.4	.02

[a] Comparison using analysis of variance (ANOVA) (continuous variables) and χ^2 statistics (categorical variable).
[b] Percentages anxiety disorders do not add up due to comorbidity.
TCAs = tricyclic antidepressants; SSRIs = selective serotonin reuptake inhibitors; SD = standard deviation; BMI = body mass index; MET = multiple of the resting metabolic rate; BAI = Beck Anxiety Inventory; nr = number.

viduals were older, had a higher mean BMI, performed less physical activity, drank less, more often used β blocking agents and other heart or blood pressure medication, had more comorbid MDD and remitted anxiety disorder diagnoses, and had a higher mean BAI score.

Although remitted and current anxious patients without antidepressant medication also differed significantly in BAI score (8.5 and 17.5, respectively), they both did not differ significantly from the controls in terms of HR, SDNN, or RSA in rest or test conditions adjusted for covariates (Table 5; Figure 1). Addition of the BAI score as a covariate did not change this outcome. In contrast, all anxiety patients on an antidepressant, with BAI scores similar to the current anxious patients without medication, had a significantly lower SDNN and RSA compared with the controls in both conditions (all $p \leq .003$ for SDNN and RSA), with effect sizes ranging between $d = 0.197$ and $d = 0.799$ with the highest effect sizes for TCA users. The antidepressants had parallel effects on HR, with the exception of SSRIs. Anxious TCA users had a significantly higher HR compared with controls with a large effect size ($d = 0.802–0.827$). Smaller HR increases were found in anxious users of other antidepressants ($p = .09–0.001$ and $d = 0.172–0.339$). In anxious SSRI users, the opposite effect was found such that HR was lower than in anxious subjects without medication, although only in the test condition ($p = .005$ and $d = 0.185$).

DISCUSSION

This large-scale cohort study showed that, when compared with healthy controls, subjects with an anxiety disorder have a significantly lower total HRV, an established risk factor for CVD (11,15,45), and significantly lower RSA, which is con-

TABLE 5. Heart Rate (bpm), RSA (ms) and SDNN (ms) per Medication Group[a]

	n	BAI Score	Heart Rate			SDNN			RSA		
			Mean ± SE	*p*	Effect Size	Mean ± SE	*p*	Effect Size	Mean ± SE	*p*	Effect Size
Rest condition											
Control	616	4	68.7 ± 0.4	REF[b]	REF[b]	77.9 ± 1.2	REF[b]	REF[b]	51.6 ± 1.1	REF[b]	REF[b]
Any remitted anxiety disorder, no medication	326	8.5	68.7 ± 0.5	.95	0.005	77.7 ± 1.6	.91	0.008	49.5 ± 1.4	.24	0.08
Any current anxiety disorder, no medication	701	17.5	68.3 ± 0.4	.54	0.035	77.0 ± 1.1	.59	0.031	49.7 ± 1.0	.19	0.074
Any anxiety disorder on TCA	60	19.9	76.4 ± 1.2	<.001	0.827	60.5 ± 3.8	<.001	0.59	32.9 ± 3.3	<.001	0.719
Any anxiety disorder on SSRI	376	19.1	68.5 ± 0.5	.74	0.022	70.6 ± 1.5	<.001	0.246	38.5 ± 1.3	<.001	0.505
Any anxiety disorder on other antidepressant	116	19.9	71.8 ± 0.9	.001	0.339	60.3 ± 2.7	<.001	0.596	33.9 ± 2.4	<.001	0.68
Test condition											
Control	616	4	73.5 ± 0.4	REF[b]	REF[b]	65.1 ± 0.8	REF[b]	REF[b]	47.6 ± 0.9	REF[b]	REF[b]
Any remitted anxiety disorder, no medication	326	8.5	73.1 ± 0.5	.58	0.038	65.8 ± 1.1	.62	0.034	45.6 ± 1.2	.18	0.091
Any current anxiety disorder, no medication	701	17.5	72.5 ± 0.3	.07	0.103	65.8 ± 0.8	.56	0.033	46.7 ± 0.8	.43	0.045
Any anxiety disorder on TCA	60	19.9	80.9 ± 1.2	<.001	0.802	48.6 ± 2.7	<.001	0.799	30.4 ± 2.8	<.001	0.79
Any anxiety disorder on SSRI	376	19.1	71.7 ± 0.5	.005	0.185	61.0 ± 1.1	.003	0.197	38.5 ± 1.1	<.001	0.417
Any anxiety disorder on other antidepressant	116	19.9	75.1 ± 0.9	.09	0.172	55.6 ± 1.9	<.001	0.463	34.8 ± 2.0	<.001	0.586

[a] Adjusted for respiratory rate, age, sex and education, body mass index, physical activity, smoking, alcohol use, heart disease, chronic disease, and heart medication.

[b] Control is the reference group. All *p* values and effect sizes are for comparison of the group in that specific line and control subjects.

RSA = respiratory sinus arrhythmia; SDNN = root mean square of successive differences; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; AD = antidepressant.

sidered to reflect the lower cardiac vagal control (46,47) that might underlie this increased risk (48). The lower HRV was not specific to PD, but was found for all anxious individuals, whether afflicted with PD, SP, or GAD. Lower HRV, especially lower cardiac vagal control, was not only observed among current anxiety patients but also among those with a remitted diagnosis. In all instances, the effect sizes were very modest, with *d* values between 0.10 and 0.25. Very similar results were found in the supine rest condition and the (much longer) active test condition.

A major aim of the study was to examine the extent to which the potential association between the presence of anxiety disorders and HRV is confounded by lifestyle and use of antidepressants, and this may have been the first study sufficiently powered to do so. Compared with all previous studies, we used a large sample of patients with remitted or current anxiety, both medicated and nonmedicated, who were ascertained in multiple ways to obtain a representative population sample of patients. In addition, the availability of prolonged ambulatory recordings of SDNN and RSA in the nearly complete sample provided us with stable and reliable indicators. Our findings showed that lower HRV in anxious subjects survived adjustment for possible confounding factors as health indicators and lifestyle, but further adjustment for antidepressant use rendered all associations nonsignificant.

Considering the effects of age on the cardiac indices, our result are in line with other studies reporting significant decreases in HR and HRV with age (49–52). In our study, females had a significantly higher HR and RSA, but lower SDNN compared with males, which is in accordance with earlier findings (50–52). Although several papers have been published on HRV and obesity, few studies have addressed the relationship between HRV and continuous BMI, and findings have been inconsistent (50,53–55). In line with Kageyama et al. (55) and Britton et al. (53), we found that an increase in BMI was significantly associated with an increase in HR and a decrease in SDNN, but the effect of BMI on RSA was not significant. We found no significant effect of smoking on HR and HRV, which concurs with some (55) but contrasts with other previous reports (56). In contrast to many smaller studies

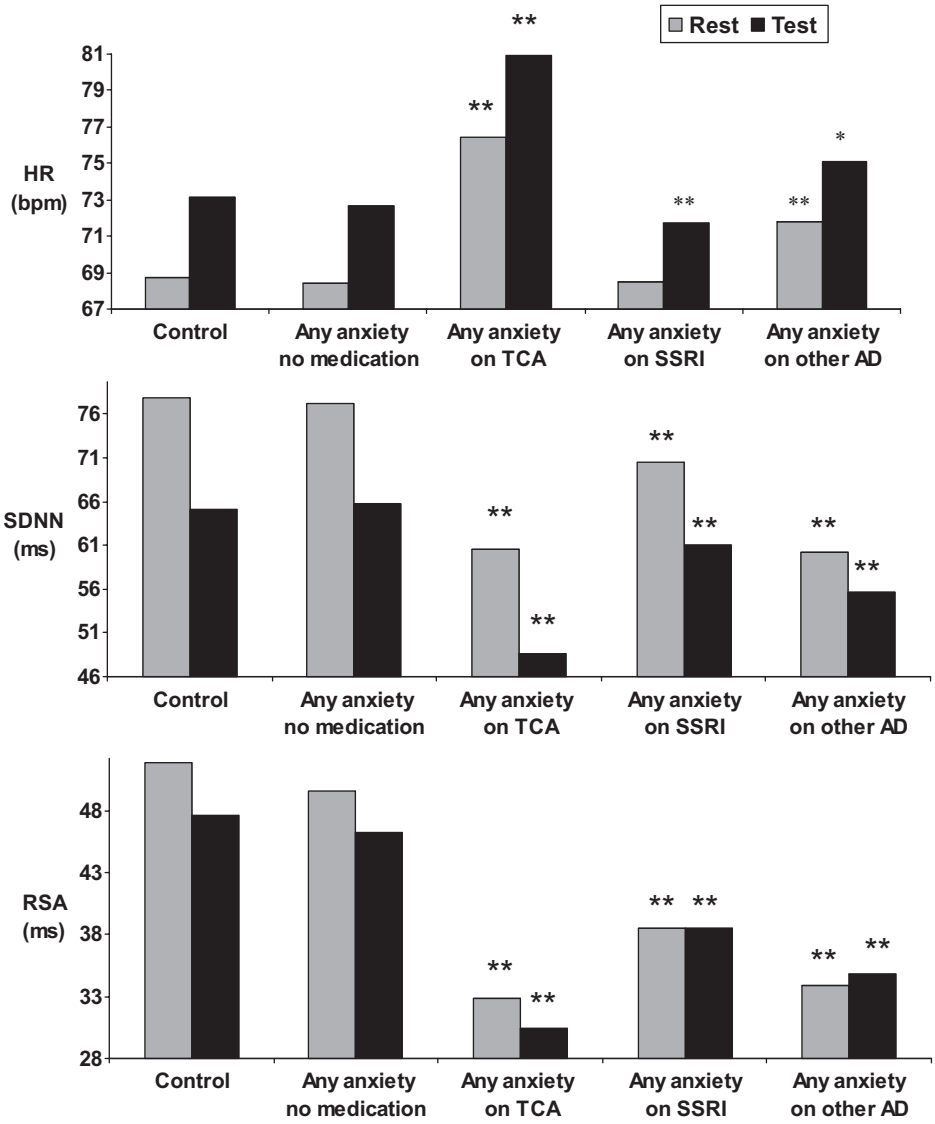

Figure 1. Heart rate (bpm), SDNN (ms) and RSA (ms) in controls, anxious subjects without medication and anxious subjects on medication. * $.05 \leq p < .10$; ** $p \leq .005$; all p values compare anxious subjects with controls. HR = heart rate; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; AD = antidepressant; SDNN = standard deviation of the normal-to-normal intervals; RSA = respiratory sinus arrhythmia.

reporting no effect or a detrimental effect of acute or chronic alcohol use on ANS functioning (55,57–61), we found that moderate and mild drinkers had a significantly higher HRV and lower HR compared with nondrinking individuals. Our results show that physically active subjects have a lower HR and higher SDNN, as observed previously (14,62,63). RSA, however, was not significantly higher in the more active individuals.

Although these lifestyle factors may act as potential confounders, multivariate analyses showed that they did not explain the lower SDNN and RSA in patients with anxiety disorders. Instead, this association seemed to be mainly driven by the effects of antidepressants. Anxious subjects receiving antidepressants showed significantly lower RSA (effect sizes between $d = 0.415$ and $d = 0.783$) and SDNN (effect sizes between $d = 0.195$ and $d = 0.792$), whereas differences between controls and anxious subjects without antidepressants were nonsignificant independent of present or past diagnosis. This effect was also independent of anxiety severity because current anxious subjects without and with medication hardly differed in BAI severity score, whereas they significantly differed in terms of HR, SDNN, and RSA. Also, additional correction for anxiety severity and comorbid MDD did not change the results. Although the effects of TCAs, which have previously been reported to have a powerful tachycardiac effect (64–66), were the most prominent (effect sizes = around 0.8), the antidepressant effects were not limited to TCAs. Consistently lower SDNN and RSA were also found in anxious patients using SSRIs (effect sizes = between 0.2 and 0.4) and other antidepressants (effect sizes = between 0.5 and 0.6).

The above results and conclusions must be weighed by some limitations of this study. First, this study was performed

during a clinic visit involving uncommon procedures, unfamiliar research assistants, and interviews with questions of a personal nature. Anxious patients may be more inclined to respond to such challenges with decreased cardiac vagal tone, and our results may have partially reflected this. It is unclear, however, how this "laboratory anxiety" can account for the observed effects of antidepressant medication on RSA and SDNN. Nonetheless, generalizability to a more familiar and less stressful real life setting cannot be assumed without actual ambulatory recording. Second, the demands of the already vulnerable participants of this large longitudinal cohort study did not allow us to add a true stress condition to the design. The test condition was not intended to be stressful and the mild decrease in HRV levels compared with supine rest should be attributed mainly to the change in posture. Therefore, we could not test the idea that ANS reactivity to stressors differs between anxious subjects and healthy controls as is implied by theoretical models like the polyvagal theory and the autonomic flexibility-neurovisceral integration model (67,68). Finally, we cannot exclude systematic differences in cardiac sympathetic control or intrinsic HR between the various groups in this study, which may have affected our measures of HRV and cardiac vagal control. Medication-specific effects on sympathetic nervous system activity, for instance, might explain why we find lower HRV in anxious subjects using SSRIs but not higher HR. To resolve this, additional measures of cardiac sympathetic control would have been needed.

In sum, our findings demonstrate that subjects with an anxiety disorder have a lower SDNN and RSA. The major part of this association was due to the effect of antidepressant use because the use of TCAs and SSRIs as well as other antidepressants had a pronounced effect on HRV. As it has been widely established that lowered HRV is a risk factor for cardiovascular morbidity and mortality (11,15,45,48), our findings of lower SDNN and RSA in antidepressant users could be of importance for clinical practice. However, cause and effect remain to be established. Before longitudinal follow-up data are available, we do not know whether the lower SDNN and RSA are caused by antidepressants and whether the low SDNN and RSA found in medicated subjects is reversed when subjects cease their medication. It is also an open question whether lower HRV found in antidepressant users is outweighed by the beneficial effects of antidepressant medication on anxiety and future heart disease.

REFERENCES

1. Albert CM, Chae CU, Rexrode KM, Manson JE, Kawachi I. Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. Circulation 2005;111:480–7.
2. Dunner DL. Anxiety and panic: relationship to depression and cardiac disorders. Psychosomatics1985;26(11 Suppl):18–22.
3. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr, Benjamin EJ. Tension and anxiety and the prediction of the 10-year incidence of coronary heart disease, atrial fibrillation, and total mortality: the Framingham Offspring Study. Psychosom Med 2005;67:692–6.
4. Frasure-Smith N, Lesperance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. Arch Gen Psychiatry 2008;65:62–71.
5. Friedman S. Cardiac disease, anxiety, and sexual functioning. Am J Cardiol 2000;86:46F–50F.
6. Friedmann E, Thomas SA, Liu F, Morton PG, Chapa D, Gottlieb SS. Relationship of depression, anxiety, and social isolation to chronic heart failure outpatient mortality. Am Heart J 2006;152:940–8.
7. Mykletun A, Bjerkeset O, Dewey M, Prince M, Overland S, Stewart R. Anxiety, depression, and cause-specific mortality: the HUNT study. Psychosom Med 2007;69:323–31.
8. Strik JJ, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. J Am Coll Cardiol 2003;42:1801–7.
9. Szekely A, Balog P, Benko E, Breuer T, Szekely J, Kertai MD, Horkay F, Kopp MS, Thayer JF. Anxiety predicts mortality and morbidity after coronary artery and valve surgery—a 4-year follow-up study. Psychosom Med 2007;69:625–31.
10. Tully PJ, Baker RA, Knight JL. Anxiety and depression as risk factors for mortality after coronary artery bypass surgery. J Psychosom Res 2008; 64:285–90.
11. Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, Schouten EG. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. Atherosclerosis risk in communities. Circulation 2000; 102:1239–44.
12. Liao D, Cai J, Rosamond WD, Barnes RW, Hutchinson RG, Whitsel EA, Rautaharju P, Heiss G. Cardiac autonomic function and incident coronary heart disease: a population-based case-cohort study. The ARIC study. Atherosclerosis risk in communities study. Am J Epidemiol 1997;145: 696–706.
13. Palatini P, Julius S. Elevated heart rate: a major risk factor for cardiovascular disease. Clin Exp Hypertens 2004;26:637–44.
14. Rosenwinkel ET, Bloomfield DM, Arwady MA, Goldsmith RL. Exercise and autonomic function in health and cardiovascular disease. Cardiol Clin 2001;19:369–87.
15. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events. The Framingham heart study. Circulation 1996;94:2850–5.
16. Fuller BF. The effects of stress-anxiety and coping styles on heart rate variability. Int J Psychophysiol 1992;12:81–6.
17. Jönsson P. Respiratory sinus arrhythmia as a function of state anxiety in healthy individuals. Int J Psychophysiol 2007;63:48–54.
18. Watkins LL, Grossman P, Krishnan R, Sherwood A. Anxiety and vagal control of heart rate. Psychosom Med 1998;60:498–502.
19. Berntson GG, Cacioppo JT, Grossman P. Whither vagal tone. Biol Psychol 2007;74:295–300.
20. Houtveen JH, Rietveld S, de Geus EJ. Contribution of tonic vagal modulation of heart rate, central respiratory drive, respiratory depth, and respiratory frequency to respiratory sinus arrhythmia during mental stress and physical exercise. Psychophysiology 2002;39:427–36.
21. Brown HN, Kemble SB. Episodic anxiety and cardiac arrhythmias. Psychosomatics 1981;22:907–15.
22. Friedman BH. An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. Biol Psychol 2007;74:185–99.
23. Cohen H, Benjamin J, Geva AB, Matar MA, Kaplan Z, Kotler M. Autonomic dysregulation in panic disorder and in post-traumatic stress disorder: application of power spectrum analysis of heart rate variability at rest and in response to recollection of trauma or panic attacks. Psychiatry Res 2000;96:1–13.
24. Klein E, Cnaani E, Harel T, Braun S, Ben-Haim SA. Altered heart rate variability in panic disorder patients. Biol Psychiatry 1995;37:18–24.
25. McCraty R, Atkinson M, Tomasino D, Stuppy WP. Analysis of twenty-four hour heart rate variability in patients with panic disorder. Biol Psychol 2001;56:131–50.
26. Yeragani VK, Balon R, Pohl R, Ramesh C, Glitz D, Weinberg P, Merlos B. Decreased R-R variance in panic disorder patients. Acta Psychiatr Scand 1990;81:554–9.
27. Cohen H, Benjamin J. Power spectrum analysis and cardiovascular morbidity in anxiety disorders. Auton Neurosci 2006;128:1–8.
28. Licht CMM, de Geus JCN, Zitman FG, Hoogendijk WJG, van Dyck R, Pennix BWJH. Association between major depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). Arch Gen Psychiatry 2008;65:1358–67.
29. Penninx BWJH, Beekman ATF, Smit JH, Zitman FG, Nolen WA, Spinhoven P, Cuijpers P, de Jong PJ, van Marwijk HWJ, Assendelft

WJJ, van der Meer K, Verhaak P, Wensing M, de Graaf R, Hoogendijk WJ, Ormel J, van Dyck R. The Netherlands study of depression and anxiety (NESDA): rationale, objectives and methods. Int J Meth Psychiatr Res 2008;17:121–40.
30. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, Walters EE, Zaslavsky AM. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med 2002;32:959–76.
31. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 2001.
32. Wittchen HU. Reliability and validity studies of the WHO—Composite International Diagnostic Interview (CIDI): a critical review. J Psychiatr Res 1994;28:57–84.
33. Steer RA, Kumar G, Ranieri WF, Beck AT. Use of the Beck anxiety inventory with adolescent psychiatric outpatients. Psychol Rep 1995;76: 459–65.
34. de Geus EJ, Willemsen GH, Klaver CH, van Doornen LJ. Ambulatory measurement of respiratory sinus arrhythmia and respiration rate 9. Biol Psychol 1995;41:205–27.
35. Willemsen GH, de Geus EJ, Klaver CH, van Doornen LJ, Carroll D. Ambulatory monitoring of the impedance cardiogram. Psychophysiology 1996;33:184–93.
36. Eckberg DL. The human respiratory gate. J Physiol 2003;548:339–52.
37. Grossman P, van BJ, Wientjes C. A comparison of three quantification methods for estimation of respiratory sinus arrhythmia. Psychophysiology 1990;27:702–14.
38. Houtveen JH, Molenaar PC. Comparison between the Fourier and Wavelet methods of spectral analysis applied to stationary and nonstationary heart period data. Psychophysiology 2001;38:729–35.
39. Goedhart AD, van der SS, Houtveen JH, Willemsen G, de Geus EJ. Comparison of time and frequency domain measures of RSA in ambulatory recordings. Psychophysiology 2007;44:203–15.
40. Greenwald AG, McGhee DE, Schwartz JL. Measuring individual differences in implicit cognition: the implicit association test. J Pers Soc Psychol 1998;74:1464–80.
41. Grossman P, Karemaker J, Wieling W. Prediction of tonic parasympathetic cardiac control using respiratory sinus arrhythmia: the need for respiratory control. Psychophysiology 1991;28:201–16.
42. Booth M. Assessment of physical activity: an international perspective. Res Q Exerc Sport 2000;71(2 Suppl):S114–S120.
43. World Health Organization, Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) classification. 2007. Ref Type: Catalog.
44. Grossman P, Kollai M. Respiratory sinus arrhythmia, cardiac vagal tone, and respiration: within- and between-individual relations. Psychophysiology 1993;30:486–95.
45. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. Circulation 1993;88:927–34.
46. Berntson GG, Cacioppo JT, Quigley KS. Respiratory sinus arrhythmia: autonomic origins, physiological mechanisms, and psychophysiological implications. Psychophysiology 1993;30:183–96.
47. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043–65.
48. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol 2007;74:224–42.
49. Agelink MW, Malessa R, Baumann B, Majewski T, Akila F, Zeit T, Ziegler D. Standardized tests of heart rate variability: normal ranges obtained from 309 healthy humans, and effects of age, gender, and heart rate. Clin Auton Res 2001;11:99–108.
50. Antelmi I, de Paula RS, Shinzato AR, Peres CA, Mansur AJ, Grupi CJ. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. Am J Cardiol 2004;93:381–5.
51. Kupper NH, Willemsen G, van den Berg M, de Boer D, Posthuma D, Boomsma DI, de Geus EJ. Heritability of ambulatory heart rate variability. Circulation 2004;110:2792–6.
52. Zhang J. Effect of age and sex on heart rate variability in healthy subjects. J Manipulative Physiol Ther 2007;30:374–9.
53. Britton A, Shipley M, Malik M, Hnatkova K, Hemingway H, Marmot M. Changes in heart rate and heart rate variability over time in middle-aged men and women in the general population (from the Whitehall II cohort study). Am J Cardiol 2007;100:524–7.
54. Wu JS, Lu FH, Yang YC, Lin TS, Huang YH, Wu CH, Chen JJ, Chang CJ. Epidemiological evidence of altered cardiac autonomic function in overweight but not underweight subjects. Int J Obes (Lond) 2008;32: 788–94.
55. Kageyama T, Nishikido N, Honda Y, Kurokawa Y, Imai H, Kobayashi T, Kaneko T, Kabuto M. Effects of obesity, current smoking status, and alcohol consumption on heart rate variability in male white-collar workers. Int Arch Occup Environ Health 1997;69:447–54.
56. Hayano J, Yamada M, Sakakibara Y, Fujinami T, Yokoyama K, Watanabe Y, Takata K. Short- and long-term effects of cigarette smoking on heart rate variability. *Am J Cardiol* 1990;65:84–8.
57. Malpas SC, Whiteside EA, Maling TJ. Heart rate variability and cardiac autonomic function in men with chronic alcohol dependence. Br Heart J 1991;65:84–8.
58. Murata K, Landrigan PJ, Araki S. Effects of age, heart rate, gender, tobacco and alcohol ingestion on R-R interval variability in human ECG. J Auton Nerv Syst 1992;37:199–206.
59. Murata K, Araki S, Yokoyama K, Sata F, Yamashita K, Ono Y. Autonomic neurotoxicity of alcohol assessed by heart rate variability. J Auton Nerv Syst 1994;48:105–11.
60. Ryan JM, Howes LG. Relations between alcohol consumption, heart rate, and heart rate variability in men. Heart 2002;88:641–2.
61. Thayer JF, Hall M, Sollers JJ III, Fischer JE. Alcohol use, urinary cortisol, and heart rate variability in apparently healthy men: evidence for impaired inhibitory control of the HPA axis in heavy drinkers. Int J Psychophysiol 2006;59:244–50.
62. Goldsmith RL, Bigger JT Jr, Bloomfield DM, Steinman RC. Physical fitness as a determinant of vagal modulation. Med Sci Sports Exerc 1997;29:812–7.
63. Rennie KL, Hemingway H, Kumari M, Brunner E, Malik M, Marmot M. Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. Am J Epidemiol 2003;158:135–43.
64. Glassman AH, Roose SP, Bigger JT Jr. The safety of tricyclic antidepressants in cardiac patients. Risk-benefit reconsidered. JAMA 1993;269: 2673–5.
65. Pacher P, Ungvari Z, Nanasi PP, Furst S, Kecskemeti V. Speculations on difference between tricyclic and selective serotonin reuptake inhibitor antidepressants on their cardiac effects. Is there any? Curr Med Chem 1999;6:469–80.
66. Slavicek J, Paclt I, Hamplova J, Kittnar O, Trefny Z, Horacek BM. Antidepressant drugs and heart electrical field. Physiol Res 1998;47: 297–300.
67. Friedman BH. An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. Biol Psychol 2007;74:185–99.
68. Porges SW. The polyvagal theory: phylogenetic substrates of a social nervous system. Int J Psychophysiol 2001;42:123–46.